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Implementing optimal allocation for sequential continuous responses with multiple treatments

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ABSTRACT

In practice, it is important to find optimal allocation strategies for continuous response with multiple treatments under some optimization criteria. In this article, we focus on exponential responses. For a multivariate test of homogeneity, we obtain the optimal allocation strategies to maximize power while (1) fixing sample size and (2) fixing expected total responses. Then the doubly adaptive biased coin design [Hu, F., Zhang, L.-X., 2004. Asymptotic properties of doubly adaptive biased coin designs for multi-treatment clinical trials. The Annals of Statistics 21, 268–301] is used to implement the optimal allocation strategies. Simulation results show that the proposed procedures have advantages over complete randomization with respect to both inferential (power) and ethical standpoints on average. It is important to note that one can usually implement optimal allocation strategies numerically for other continuous responses, though it is usually not easy to get the closed form of the optimal allocation theoretically.

1. Introduction

Response-adaptive randomization (RAR) procedures assign subjects to one of the K treatments with probabilities according to previous treatment assignments and responses in order to meet some objectives (Hu and Rosenberger, 2006). Ideally, one can use the following three steps to implement optimal RAR procedures in practice. The first is to determine the main objectives and formulate these objectives mathematically. The second is to find the target allocation proportion which achieves these objectives. The third is to use some RAR procedures to target the optimal allocation proportion. The first step is usually based on the real problem in practice. We will focus on the second and third steps in this paper.

For the second step, there are a lot of discussions for comparing two treatments in the literature. For example, Neyman allocation is obtained by maximizing power. Rosenberger et al. (2001) find the allocation which minimizes the expected total failures for fixed power. A general optimization is discussed in Jennison and Turnbull (2000), and it can be traced back to ideas of Hayre (1979). Recently, Tymofyeyev et al. (2007) have established a general mathematical framework to obtain optimal allocations. For binary responses, they successfully derive the optimal allocations for maximizing power with K treatments for fixed sample size.

Eisele (1994) and Eisele and Woodroofe (1995) describe a doubly adaptive biased coin design (DBCD). Hu and Zhang (2004) provide a broad family of RAR procedure. This family encompasses any procedure with a target allocation which is a function of unknown parameters. Therefore, the DBCDs can be used to target the optimal allocation proportion. Hu and Rosenberger (2003) and Rosenberger and Hu (2004) study many procedures including those above for binary responses to conclude that Hu and Zhang's procedure is the best one to maintain power while targeting any specific allocation proportion.

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Most attention has been focused on binary responses in the literature (see Rosenberger et al., 2001; Tymofyeyev et al., 2007). However, there are many clinical trials with continuous responses. For example, the exponential distribution is commonly used in life-testing. In particular, when the disease has a rapid progression to death such as severe viral hepatitis, the exponential distribution fits the data very well. Its application can be found in Zelen (1966), Feigl and Zelen (1965), Byar (1974), Louis (1977), DeWals and Bouckaert (1985), and Shulz et al. (1986).

It is usually difficult to obtain optimal allocation proportions for continuous responses with more than two treatments. In this paper, we discuss the optimal allocation for the exponential responses with multiple treatments based on the framework proposed by Tymofyeyev et al. (2007). Then we use Hu and Zhang's procedure to implement the optimal allocation proportions. The main advantages of proposed procedures over complete randomization (CR) are: (i) more powerful and (ii) more ethical (by sending more patients to the better treatment). These advantages are demonstrated both theoretically and numerically.

We focus on responses from exponential distribution in this paper. The same approach works for other continuous responses. The main contributions of this paper are: (i) a closed form of optimal allocation for maximizing the power with fixed sample size for K treatments; (ii) a closed form of optimal allocation for maximizing the power with fixed expected total responses for three treatments; and (iii) implementing the optimal allocation proportions by using Hu and Zhang's procedure and showing the advantages over CR.

Tymofyeyev et al. (2007) only derived the optimal results for maximizing power with fixed sample size for binary responses. In this paper, we obtain optimal allocation proportions for maximizing the power with both fixed sample size (for K treatments) and fixed expected total responses (for $K=3$ treatments). The latter is usually difficult to prove and the proof itself brings some insight to future research in this topic. Also comparing three treatments is quite common in practice. The closed form results in Theorems 1 and 2 provide a necessary and essential foundation for further theoretical analysis of the procedure (see Hu et al., 2006). It is worth noting that the closed form of the optimal allocation proportions is sometimes hard to obtain. In these situations, one can usually find optimal proportions numerically. Then Hu and Zhang's procedure can be used to implement them. However, it is then difficult to study further theoretical properties without the closed form.

The article is organized as follows. Section 2 describes the statistical hypothesis and the optimization problems. Then we state the two closed forms of the optimal allocation mentioned above. In Section 3, Hu and Zhang's procedure is used to implement the optimal allocation proportion. Numerical studies are reported. Concluding remarks are in Section 4. The proofs are relegated to the Appendix.

2. Optimization

2.1. Hypothesis and optimization problem

We assume that the responses of K treatments are from exponential distribution with mean $\beta_1, \ldots, \beta_K$, respectively, and we want to test the null hypothesis of homogeneity $H_0 : \beta_1 = \beta_2 = \cdots = \beta_K$. By Lachin (2000)'s overview of some alternative hypothesis for multivariate test, the contrast test of homogeneity which compares $K-1$ treatments to a control is one natural choice. This alternative is useful in many applications. Mathematically the hypothesis is $H_0 : \boldsymbol{\beta_c} = 0$ versus $H_A : \boldsymbol{\beta_c} \neq 0$ where $\boldsymbol{\beta_c} = (\beta_1 - \beta_K, \beta_2 - \beta_K, \ldots, \beta_{K-1} - \beta_K)$.

Let $\hat{\boldsymbol{\beta}}_{\boldsymbol{c}}$ be the maximum likelihood estimator (MLE) of $\boldsymbol{\beta_c}$. Let $\mathbf{n} = (n_1, \ldots, n_K)$, where n_k is the number of the subjects who are assigned to the treatment k, $k = 1, 2, \ldots, K$ and the sample size $n = n_1 + n_2 + \cdots + n_K$. Then the variance–covariance matrix of $\hat{\boldsymbol{\beta}}_{\boldsymbol{c}}$ is

$$\boldsymbol{\Sigma_n} = \begin{pmatrix} \beta_1^2/n_1 & 0 & \ldots & 0 \\ 0 & \beta_2^2/n_2 & \ldots & 0 \\ \ldots & \ldots & \ldots & \ldots \\ 0 & 0 & \ldots & \beta_{K-1}^2/n_{K-1} \end{pmatrix} + \frac{\beta_K^2}{n_K}\mathbf{1}\mathbf{1}',$$

where $\mathbf{1} = (1, 1, \ldots, 1)'$.

The test statistic is $\hat{\boldsymbol{\beta}}_{\boldsymbol{c}}'\hat{\boldsymbol{\Sigma}}_n^{-1}\hat{\boldsymbol{\beta}}_{\boldsymbol{c}}$, where $\hat{\boldsymbol{\Sigma}}_{\boldsymbol{n}}$ is a consistent estimator of $\boldsymbol{\Sigma_n}$ by substituting $\hat{\beta}_i$, $i = 1, \ldots, K$. This statistic asymptotically follows a chi-square distribution with $K-1$ degree of freedom under the null hypothesis. Under the alternative hypothesis, the distribution is noncentral chi-squared with noncentrality parameter given by

$$\phi(\mathbf{n}) = \boldsymbol{\beta_c}'\boldsymbol{\Sigma_n}^{-1}\boldsymbol{\beta_c} = \sum_{j=1}^{K-1} \frac{n_j}{\beta_j^2}(\beta_j - \beta_K)^2 - \left(\sum_{j=1}^{K-1} \frac{n_j}{\beta_j^2}(\beta_j - \beta_K)\right)^2 \Bigg/ \sum_{j=1}^{K} \frac{n_j}{\beta_j^2}. \tag{1}$$

Obviously, the larger the $\phi(\mathbf{n})$ is, the larger the power is.